Psychopharmacology (1998) 135 : 213–229

ORIGINAL INVESTIGATION

**John H. Krystal · Laurence P. Karper · Alexandre Bennett
D. Cyril D'Souza · Anissa Abi-Dargham · Kristen Morrissey
Danielle Abi-Saab · J. Douglas Bremner · Malcolm B. Bowers Jr
Raymond F. Suckow · Philip Stetson · George R. Heninger
Dennis S. Charney**

Interactive effects of subanesthetic ketamine and subhypnotic lorazepam in humans

Received: 1 April 1996/Final version: 20 May 1997

Abstract Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist with psychotogenic and dissociative effects in healthy humans. These cognitive and perceptual effects in humans are reportedly reduced by benzodiazepine premedication. This study assessed the interactive effects of a ketamine (IV bolus of 0.26 mg/kg followed by an infusion of 0.65 mg/kg per hour) and lorazepam 2 mg., PO, in humans. Twenty-three healthy subjects completed 4 test days involving the oral administration of lorazepam or matched placebo 2 h prior to the IV infusion of ketamine or placebo. Ketamine: 1) produced behaviors similar to the positive and negative symptoms of schizophrenia as assessed by the Brief Psychiatric Rating Scale (BPRS); 2) evoked perceptual alterations as measured by the Clinician-Administered Dissociative States Scale (CADSS); 3) impaired performance on the Wisconsin Card Sorting Test (WCST) and other tests sensitive to frontal cortical impairment; and 4) had amnestic effects. Lorazepam produced attention impairments, concrete proverb interpretations, and recall impairments. Lorazepam reduced ketamine-associated emotional distress and there was a non-significant trend for it to decrease perceptual alterations produced by ketamine. However, it failed to reduce many cognitive and behavioral effects of ketamine, including psychosis. Further, lorazepam exacerbated the sedative, attention-impairing, and amnestic effects of ketamine. There was no evidence of pharmacokinetic interaction between these medications. These data suggest that subhypnotic lorazepam and ketamine show a spectrum of interactive effects, ranging from antagonism to potentiation.

Key words Ketamine · *N*-methyl-D-aspartate · Glutamate · Psychosis · Dissociation · GABA · Benzodiazepine · Memory · Attention · Frontal cortex · Wisconsin Card Sorting Test

J.H. Krystal · L.P. Karper · A. Bennett · D.C. D'Souza
A. Abi-Dargham · J.D. Bremner · M.B. Bowers Jr
G.R. Heninger D.S. Charney
Department of Psychiatry, Yale University School of Medicine, Connecticut, USA

J.H. Krystal (✉) · L.P. Karper · A. Bennett · D.C. D'Souza
A. Abi-Dargham · K. Morrissey · D. Abi-Saab · J.D. Bremner
D.S. Charney
Psychiatry Service (116-A), VA Medical Center,
West Haven, CT 06516, USA

J.H. Krystal · G.R. Heninger
Abraham Ribicoff Research Facilities,
Connecticut Mental Health Center, 34 Park Street,
New Haven, CT 06519, USA

A. Bennett
Department of Neurology,
Cornell University Medical Center New York,
New York, USA

M.B. Bowers Jr
Grace Education Building, 25 Park Street,
New Haven, CT 06510, USA

R.F. Suckow
New York State Psychiatric Institute, 722 W. 168th Street,
New York, NY 10032, USA

P. Stetson
Upjohn Center for Clinical Pharmacology,
University of Michigan Medical Center,
Ann Arbor, MI 48109-0504, USA

Introduction

There is growing interest in the human psychopharmacology of *N*-methyl-D-aspartate (NMDA) receptor function in light of evidence implicating glutamate in higher cortical functions and psychiatric illness (Kim et al. 1980; Deutsch et al. 1989; Carlsson and Carlsson 1990; Javitt and Zukin 1991; Olney and Farber 1995). The NMDA receptor subclass is the site of action of PCP and ketamine (Anis et al. 1983). These drugs bind non-selectively to NMDA receptor subtypes (Anis

et al. 1983; Yamakura et al. 1993; Bresink et al. 1995). At subanesthetic doses, PCP is a selective noncompetitive NMDA antagonist (Javitt and Zukin 1991). Ketamine is 10–50 times less potent than PCP in binding to the NMDA receptor (Hampton et al. 1982), blocking NMDA-mediated neurotoxicity (Rothman and Olney 1987), seizures (Willetts et al. 1990), physiological effects (Byrd 1987), and in substituting for phencyclidine in drug discrimination paradigms (cf. Javitt and Zukin 1991). Ketamine is clinically available as a racemic mixture of two enantiomers. The *S*-isomer has 2–4 times greater affinity and selectivity for the NMDA receptor and greater clinical potency than the *R*-isomer (Øye et al. 1991, 1992; Zeilhofer et al. 1992).

NMDA antagonists have been of great interest to psychiatry because their behavioral effects resembled aspects of schizophrenia and dissociative states (Luby et al. 1959; Domino et al. 1965; Øye et al. 1992; Krystal et al., 1994; Malhotra et al. 1996). These drugs also received attention as drugs of abuse (Siegel 1978; Smith et al. 1978). Recently, the subanesthetic dose-related effects of ketamine in healthy humans were characterized using measures employed in the assessment of schizophrenia and dissociative states (Krystal et al. 1994; Malhotra et al. 1996). Ketamine produced 1) positive symptoms of psychosis, such as illusions, disturbances in thought organization, and delusions; 2) negative symptoms similar to those associated with schizophrenia, including blunted emotional responses, emotional detachment, and psychomotor retardation; 3) perceptual alterations reminiscent of dissociative states, such as slowing of time perception, altered body perception, depersonalization, derealization, and distorted sensory perception; 4) impairments on tests of frontal cortical function including increased distractibility, reduced verbal fluency, and poorer performance on the Wisconsin Card Sorting Test; and 5) learning impairments dependent on the dose of ketamine and the duration between stimulus presentation and testing. These ketamine responses are similar to the "emergence phenomena" associated with waking from ketamine anesthesia including perceptual alterations, vivid dreams, and delirium (Knox et al. 1970; Collier 1972; White et al. 1982) that limit its clinical anesthetic utility.

Benzodiazepine premedication is an established strategy for reducing dysphoric symptoms associated with emergence from ketamine anesthesia (Coppel et al. 1973; Dundee et al. 1979; Zsigmond and Domino 1980; White et al. 1982). The benzodiazepines diazepam (Kothary and Zsigmond 1977; Tucker et al. 1984), flunitrazepam (Freuchen et al. 1976), lorazepam (Dundee and Lilburn 1978; Lilburn et al. 1978), and midazolam (White 1982; Cartwright and Pingel 1984; Toft and Romer 1987; Restall et al. 1988) have been reported to reduce the emergence phenomena. Further, administration of the benzodiazepine receptor antagonist, flumazenil, increases emergence phenomena in patients treated with midazolam and ketamine (Restall et al. 1990). Benzodiazepines have also been reported to reduce the psychotogenic effects of PCP intoxication (Smith et al. 1978).

Although benzodiazepines clearly increase ketamine tolerability, methodological shortcomings of the published literature limit precise conclusions regarding the interactive cognitive and behavioral effects of these drugs . Few published studies employed double-blind designs or randomized assignment to groups (Kothary and Zsigmond 1977; Freuchen et al. 1976; White 1982). Also, only one study used a validated rating scale for assessing hallucinatory behavior (Migály et al. 1991). In addition, many reports employed retrospective symptom assessments (Cartwright and Pingel 1984; Tucker et al. 1984; Toft and Romer 1987; Restall et al. 1988). Retrospective reports are suspect for studies evaluating the interactive effects of ketamine and benzodiazepines because both agents have potent amnestic effects (White 1982; Ghoneim et al. 1984, 1985; Roache and Griffiths 1987; Øye et al. 1992; Krystal et al. 1994). In addition, the published studies did not insure that emergence symptoms were assessed at identical ketamine blood levels in patients receiving ketamine or ketamine plus benzodiazepines. Benzodiazepine co-administration may increase the duration of somnolence following ketamine administration (Dundee and Lilburn 1978). As a result, emergence symptoms may have appeared to be reduced in benzodiazepine-treated patients because awakening occurred at lower ketamine blood levels. The methodologic limitations of the published reports are of particular concern because several studies suggest that subhypnotic benzodiazepine doses do not prevent ketamine emergence phenomena (Bovill et al. 1971; Loh et al. 1972; Pandit et al. 1980).

The current study assessed the interactive effects of subanesthetic ketamine and subhypnotic lorazepam in humans in a double-blind placebo-controlled design. It evaluated the capacity of lorazepam to reduce the psychotogenic, dissociative, cognitive, physiologic, and neuroendocrine effects of ketamine in humans. This study administered ketamine as an initial bolus followed by a slow infusion in order to sustain ketamine effects during the assessment period. A subhypnotic and routinely prescribed clinical dose of oral lorazepam, 2 mg, was selected in order to avoid excessive sedation that would interfere with cognitive assessments.

Materials and methods

Subjects

Subjects were recruited for participation in this study through public advertisement and paid for their participation. Healthy subjects

were selected for participation after obtaining written informed consent and following a two-step process to exclude individuals with a history of psychiatric illness, substance abuse disorders, or significant current life stress. The first step involved the administration of a structured diagnostic interview for non-patient populations (Spitzer et al. 1990) supplemented by a clinical interview that further evaluated personal and family history. Based on this assessment, subjects were excluded who gave evidence of a psychiatric or substance abuse disorder, history of clinical consultation for an emotional difficulty, psychiatric illness in a first degree relative, or clinically significant current life stress defined operationally as 3 or greater on the Severity of Psychosocial Stressors Scale for Adults employed in axis IV of DSM-III-R (American Psychiatric Association 1987). The second step was a telephone interview conducted with an individual identified by the subject to confirm information collected from the subject. Subjects were instructed to abstain from consuming psychoactive substances for 4 weeks prior to testing. Urine toxicology screens at initial screening and on test days provided additional confirmatory evidence. None of the subjects reported a history of serious medical illness. All of the subjects had normal results on physical examination and laboratory testing, including liver and thyroid function tests. Subjects were all within normal limits on two measures of vulnerability to psychosis, the Bell Reality Testing Inventory [Hallucinations & Delusions: -0.4 ± 0.0 (SEM); Reality Distortion: -0.6 ± 0.0; Uncertainty of Perception: -0.9 ± 0.1; Bell et al. 1985] and the Wisconsin Scales of Psychosis Proneness (23.5 ± 2.1; Chapman et al. 1982).

Nineteen male (age: 29.3 ± 1.8 year; weight: 84.6 ± 4.2 kg) and 11 female subjects (age: 31.3 ± 2.9 year; weight: 70.5 ± 12.2 kg) entered the study. General intellectual capacities were comparable in the men and women participating in the study as assessed by the Slosson Intelligence Test (men: 135.0 ± 3.9; women: 133.1 ± 4.4; Slosson, 1963). Except when reported, significant gender differences did not emerge in the data analysis. Thus, unless indicated, data were collapsed across genders. Educational status of subjects was as follows: two subjects were completing post-doctoral training, 13 subjects were in graduate or professional school, 11 subjects had completed college, and two subjects had completed high school. Twenty-three subjects were Caucasian, four subjects were African-American, two subjects were of Hispanic descent, and one subject was of Asian descent. Seven subjects entering the study did not proceed to completion: two subjects were terminated due to poor venous access, one subject was excluded after revealing an exclusionary medical condition following his third test day, two subjects left the study because they found ketamine effects unpleasant, and two subjects withdrew due to scheduling difficulties. On their first day, 11 subjects received placebo lorazepam and placebo ketamine (placebo day), eight subjects received placebo lorazepam/active ketamine (ketamine day), six subjects received active lorazepam/active ketamine (ketamine-lorazepam day), and five subjects received active lorazepam/placebo ketamine (lorazepam day).

Ketamine test procedures

Ketamine administration

Subjects completed 4 test days in a randomized and balanced order under double-blind conditions during which they received lorazepam (2 mg, PO, Wyeth-Ayerst, Philadelphia, PA USA) or matched placebo 2 h before they were administered saline (0.9% NaCl, USP) or ketamine hydrochloride (Parke-Davis, Kalamazoo, Mich., USA) as a 1-min IV bolus of 0.26 mg/kg followed by a 1-h IV infusion of 0.65 mg/kg. Test days were spaced by 3–7 days. The ketamine dose and administration schedule selected in this study was based on our efforts to produce a constant ketamine blood level throughout the study period that was similar to the estimated peak blood level of our previous study (Krystal et al. 1994).

Behavioral ratings

Symptoms and behaviors characteristic of schizophrenia were assessed using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962). The BPRS previously was sensitive to ketamine effects in humans (Krystal et al. 1994). Four key BPRS items were selected as an index of the positive symptoms of schizophrenia based on previous reports indicating their utility and validity (Bowers et al. 1980; Kane et al. 1988; Krystal et al. 1993) and inclusion within the empirically-derived thought disorder factor of the BPRS (Hedlund and Vieweg 1980). These four key positive symptoms were conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content. In evaluating hallucinatory behavior, bizarre perceptual experiences associated with an identifiable sensory reference were rated as illusory perceptual alterations rather than hallucinations. This definition was more conservative than that employed in a previous report (Krystal et al. 1994) and selected to provide greater clarity in data interpretation. Three key BPRS items, blunted affect, emotional withdrawal, and motor retardation were selected as a measure of the negative symptoms of schizophrenia based on a report of their reliability and validity (Thiemann et al. 1987) and their inclusion within the empirically derived withdrawal-retardation factor of the BPRS (Hedlund and Vieweg, 1980). Activation and anxious depression were also assessed using factors derived from the BPRS (Hedlund and Vieweg 1980). The items associated with the activation factor were tension, mannerisms and posturing, and excitement. The items contributing to the anxious depression factor were anxiety, guilt feelings, depressive mood, somatic concern, tension, and motor retardation.

Anxiety, drowsiness, high, irritability, and sadness were assessed using visual analog scales completed by clinician raters. These scales were scored in millimeters from the left hand side of a 100 mm line to a perpendicular mark made by the clinician at a point corresponding to the apparent magnitude of the feeling state reported and exhibited by the subject (range: 0, "not at all," to 100, "most ever"; Charney et al. 1987). The BPRS and analog scales were administered prior to lorazepam (-120 min) and ketamine (-15 min) administration, and 5, 60, 90, 120 and 180 min following the initiation of ketamine infusion. Ratings assessed the period following the previous assessment. Thus, the 90-min timepoint reflected the previous 30 min.

The Clinician-Administered Dissociative States Scale (CADSS; Bremner et al., in review) was a clinician-administered measure of perceptual, behavioral, and attention alterations occurring during dissociative experiences which had been validated in healthy subjects, schizophrenic patients and patients with post-traumatic stress disorder. This scale involved 19 self-report questions and eight observer ratings scored from 0 (not at all) to 4 (extremely). In order better to characterize dissociative responses to ketamine, CADSS items were sorted into five subscales with apparent face validity (Krystal et al. 1994) and based on published scales assessing dissociative states (Sanders 1986; Steinberg et al. 1990): body perception, environmental perception, feelings of unreality, memory impairment, and time perception (items in each subscale available upon request). The CADSS was administered at the -150-, 5-, 60-, 90-, 120-, and 180-min timepoints.

For the memory assessment, separate sets of three words, selected on the basis of their comparable frequency of use in the English language and comparable difficulty (Kucera and Francis 1967), were presented at each timepoint. Thus, each set of words was presented once, but recall was assessed three times: immediately following presentation, following a distracting task, and following a 10-min delay. Word lists were presented 150 min prior to ketamine infusion and at the 5-, 90-, 120-, and 180-min timepoints.

A spectrum of functions associated with the frontal cortex were assessed in this study including vigilance to visual stimuli, distractibility, verbal fluency, abstraction, and the Wisconsin Card Sorting Test (Goldstein 1949; Milner 1964; Benton 1968; Salmaso and Denes 1982; Wilkins et al. 1987). Vigilance to visual stimuli was measured using a continuous performance task (Gordon 1983)

in which subjects attended to numbers presented sequentially on a screen. The subject pushed a button to signal when a "9" was preceded by a "1". The distractibility task was identical to the vigilance task with the exception that numbers were presented sequentially in three contiguous columns. Subjects had to attend to the middle column and ignore the numbers presented in the outer two columns. The verbal fluency task requires subjects to generate as many words as possible beginning with a specified letter during a 1-min interval. Equivalent versions of this task were administered on the 4 test days using letters equated for frequency in English (Borkowski et al. 1967).

Abstraction and thought disorder were evaluated by assessing the interpretation of proverbs (Gorham 1956). The scoring system described by Gorham has been modified to increase inter-rater reliability and to assess concrete and bizarre responses. The concreteness and bizarreness of each response was rated on a three-point scale where a value of zero indicated abstract and typical responses and a value of two reflected concrete and highly unusual responses. In addition, failure to respond was coded to reflect whether the subject did not respond secondary to time limitations, physical illness, or refusal. The abstract and bizarre totals were weighted to reflect the total number of responses they represent.

The Wisconsin Card Sorting Test (WCST) is a task in which cards are sorted by the number, color, and shape of objects depicted on the card. This task requires the subject to determine the rule governing the matching of cards and to adapt when these rules shift during the task. Patients with frontal lobe lesions (Milner 1964) exhibit increased perseverative error and fewer categories successfully completed on this task. Computerized versions of the WCST activated the frontal cortex in healthy subjects in a previous study (Weinberger et al. 1986). The current study utilized a computerized version of the WCST developed and validated by Dr. Donald Quinlan (unpublished data) and employed in a previous ketamine study (Krystal et al. 1994). The frontal cortical tasks were presented in a fixed order in order to increase comparability between test days. The verbal fluency, vigilance and distractibility tests, and the proverb tests were initiated 10 min following the ketamine bolus. The WCST was administered 40 min following the ketamine bolus.

In order to assess psychomotor function, the rate of finger-tapping was assessed using a telegraph key apparatus (LaFayette Instrument Co., Lafayette, Ind., USA; Halstead 1947). Subjects were instructed to tap as rapidly as possible for 10 s using their index finger. Subjects completed five successful trials, defined as within 10% of the mean of the remaining trials, with each hand alternating between dominant and non-dominant hands. Brief rest period were inserted between every three tapping trials. The meaned score of the five successful trials are reported. Subjects completed up to ten trials in order to produce five successful trials. If consistency could not be established, the five highest scores were reported. Handedness was determined using the cerebral dominance item of the Neurological Evaluation Scale (Buchanan and Heinrichs 1989). Twenty-five subjects were right-handed, four subjects were left-handed, and one subject showed mixed dominance on the basis of this evaluation. Of the 23 subjects who completed 4 test days, one was excluded from the finger tapping test due to mixed dominance.

Biochemical methods

Plasma levels of prolactin, cortisol, homovanillic acid (HVA), and lorazepam were determined. Radioimmunoassay kits were utilized for determining plasma levels of prolactin [Serono Diagnostics, Inc Norwell, Mass., USA; intra-assay and interassay coefficients of variance (CVs) were 3%, and 7%, respectively], cortisol (Baxter Travenol Diagnostics, Inc., Incstar Corp, Stillwater Minn., USA; intra-assay and interassay variance were 3% and 5%, respectively). Plasma samples for hormonal analysis were run in duplicate pairs. Plasma free levels of HVA (Bacopoulos et al. 1979) were measured by gas chromatography and mass spectrometry using deuterated internal standards.

Plasma lorazepam was determined by high performance liquid chromatography (HPLC) by one of the authors (RS.). A 1-ml aliquot of plasma containing 40 ng of internal standard oxazepam was made alkaline with 1 ml of 0.6 M carbonate buffer (pH = 9.8). Methyl-tert-butyl ether: *n*-heptane 60:40 (v/v), 5 ml was added and the contents mixed for 10 min. Following centrifugation at 1500 g for 10 min, the organic layer was transferred to a tapered centrifuge tube and dried under vacuum with moderate heat (45°C). The residue was reconstituted with 250 µl of mobile phase, vortexed and transferred to small glass inserts suitable for an autosampler. Chromatographic separation was achieved using trimethylsilyl (LC-1, Supelco) reversed phase column and a mobile phase consisting of 70% 0.05 M KH_2PO_4 and 30% acetonitrile with 1.2 ml triethylamine and 5.0 ml 20% heptane sulfonate added per liter. The pH was adjusted to 3.0 with 1 ml of 85% phosphoric acid. The flow rate was 2.0 ml/min, which resulted in retention times of 4.7 and 5.4 minutes for oxazepam and lorazepam, respectively. An ultraviolet absorbance detector set at 230 nm permitted a linear response in the lorazepam concentration range of 3–150 ng/ml. The accuracy and precision of the method was assessed by processing 12 tubes of four different concentrations (150, 50, 12.5, and 3.0 ng/ml) of lorazepam. The resulting values indicate acceptable accuracy and precision: 151 ng/ml, CV = 0.6%; 51 ng/ml, CV = 0.8%; 12.7 ng/ml, CV = 7.4%; 3.1 ng/ml, CV = 14.2%. The recovery of lorazepam from plasma did not vary within the concentration range (150 ng/ml: 79.0 ± 2.6%; 50 ng/nl: 79.0 ± 1.3%; 12.5 ng/nl: 78.0 ± 2.3%; $n = 10$ for each concentration). Inter-assay variability based on three levels of quality controls (100, 25, 5 ng/nl) resulted in values of 105 ng/ml, CV = 3.7%; 27 ng/ml, CV = 8.0%, and 4.9 ng/ml, CV = 4.9% ($n = 10$ days).

Plasma ketamine levels were determined by gas chromatography-mass spectrometry (GC/MS) by one of the authors (PS.) in seven of the subjects. In preparing the samples, 1.0 ml of plasma was added to 0.5 ml borate buffer (0.1 M, pH = 9.5) and 50 µl (500 ng) internal standard (o-Br-ketamine). The samples were vortexed and 5.0 ml benzene was added. Samples were then vigorously shaken for 10 min and centrifuged at 850 g for 10 min at room temperature. A 4-ml benzene phase aliquot was transferred to disposable glass tubes and evaporated to dryness at 40°C. The residue was dissolved in 0.2 ml methanol and transferred to conical-bottomed screw-cap reaction vials and evaporated to dryness. Pentafluoropropionic acid anhydride (PFPAA) 40 µl was then added to each vial, vortexed, tightly capped and incubated at 65°C for 30 min. After cooling to room temperature, the derivatized sample from each vial was transferred to autosampler vials for injection and GC/MS analysis. For the chromatographic analysis, the derivatized ketamine samples were analyzed on a Hewlett-Packard Model 5987A GC/MS equipped with electron impact (EI) ionization, selected ion monitoring (SIM) and autosampler. An HP Ultra Performance fused-silica capillary column (20 mm × 0.31 mm i.d.) coated with crosslinked methyl silicone to film thickness of 0.17 µM used for chromatographic separation of the sample components. The carrier gas was helium at a flow rate of 1.0 ml/min. Instrument temperature zones were: injection port (250°C), interface oven (275°C), GC interface probe (275°C), and ion source (200°C). The column oven was set at an initial temperature of 200°C for 0.1 min, then increased at 4°C/min to 230°C, where it was held for 0.5 min. Total run time was 8.1 min. The MS settings were: multiplier voltage (2300 V), emission current (300 µA), electron energy (70 eV) and ion detection in SIM mode. The mass ion specific for both ketamine and the IS (bromo-ketamine, 160 M/Z) was monitored in SIM mode from 2.5 to 8.1 min. For data acquisition, the total ion chromatogram was plotted and the ion abundance peak heights were measured. The ketamine/internal standard peak height ratios were then used to quantitate plasma ketamine levels. Calibration curves were constructed by plotting the ion abundance peak height ratios as a function of the ketamine concentration. These data were then fit to the ln-quadratic equation: $\ln(Y) = b_0 + b_1\ln(X) + b_2[\ln(X)]^2$ with a least squares regression analysis. The ketamine concentrations of unknown samples were calculated using

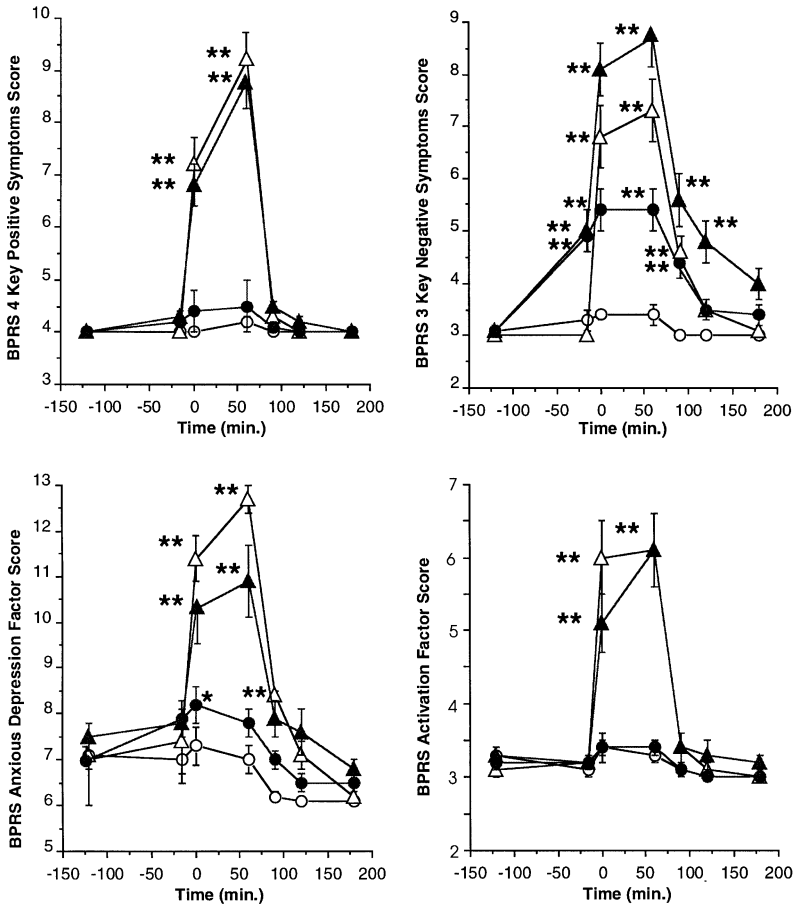

Fig. 1 Ketamine and lorazepam effects on the brief psychiatric rating scale (BPRS) in healthy subjucts ($n = 23$). Data from the BPRS four key positive symptoms, three key negative symptoms, activation factor, and anxious depression factor, are presented (*clockwise from upper left corner*). Data are presented as mean values ± SEM. Significant increases from baseline by Dunnett's multiple *t*-tests are indicated: $*P < 0.05$; $**P < 0.01$. All other statistics are presented in the text. Test days are depicted as follows: (○) placebo, (△) ketamine, (▲) ketamine-lorazepam, and (●) lorazepam

the results of the regression analyses. Under the described chromatographic conditions, the retention times for ketamine and o-Br-ketamine were 5.2 and 6.2 min, respectively. Calibration curve samples were prepared in triplicate by spiking 1.0 ml blank plasma with the appropriate volume of ketamine standard solution to achieve 20.0, 50.0, 100.0, and 500.0 ng ketamine/ml plasma. The accuracy and precision of the method were assessed by seeding quality control samples at drug concentrations of 50 and 200 ng ketamine/ml. Triplicate quality control samples were assayed on each of 3 consecutive days. The precision of the assay was found to have coefficients of variation ranging between 3.7% and 4.9%. The concentration means for the seeded control samples were found to be within 1.3% and 3.1% of the theoretical values.

Data analysis

Data were initially subjected to a repeated measures analysis of variance (RMANOVA) with within-subjects factors of ketamine (ketamine versus placebo), lorazepam (lorazepam versus placebo), and time. In the presentation, when drug (ketamine or lorazepam), time, and the drug by time interactions were all significant, only the drug by time interactions were reported. The interactive effects of gender was studied as a between-subjects factor added to the RMANOVAs. Similarly, the interactive impact of emesis on neuroendocrine data was studied by adding the presence or absence of this behavior as a between-subjects factor in the repeated measures ANOVAs. When either drug by time interaction was significant, post-hoc multiple comparisons of post-infusion timepoints to baseline were conducted using the Dunnett's multiple *t*-test (Winer 1971). Post-hoc within-subjects contrasts were employed to compare test days for data from cognitive tasks administered once per test day. Comparison of baseline values were conducted using paired *t*-tests with Bonferroni corrections to adjust for multiple comparisons. Ketamine effects on the WCST show significant order effects (Krystal et al., in preparation). As a result, Wisconsin Card Sorting Test data in this report are solely from the first test day for each subject. These data were compared using an ANOVA in a between subjects design. Post-hoc testing of Wisconsin Card Sorting Test results were conducted using the Fisher Protected Least Significant Difference (PLSD) multiple comparison test. The relationship between baseline demographic and descriptive data and peak change post-infusion at the highest dose of ketamine was explored using Pearson correlations.

Results

Brief Psychiatric Rating Scale (BPRS)

Positive symptoms

As indicated in Fig. 1, ketamine produced an increase in the four key positive symptoms of schizophrenia in healthy subjects ($n = 23$). However, lorazepam did not significantly modulate the severity of these ketamine-induced symptoms. In the RMANOVA, the interactive effects of ketamine and time ($F_{6,132} = 73.2$, $P = 0.0001$) were significant. Lorazepam did not significantly alter BPRS positive symptoms. There were no significant differences in baseline scores between test days.

Ketamine increased three of the four positive symptoms, but none of the drug interaction effects attained significance. In the RMANOVA, ketamine (ketamine by time interaction: $F_{6,132} = 84.6$, $P = 0.0001$), but not lorazepam, increased scores on the conceptual disorganization item. Conceptual disorganization was manifest in a variety of ways including altered rate of thoughts, increased tangentiality, and loosening of associations. For example, one subject reported "I can empathize with Kramer on Seinfeld, it's like I'm floating across the Tundra, I feel like I'm going to say everything that goes through my mind. I feel like I'm going back and forth like I'm in an earthquake. I'm tangential. I can see 180 degrees. Do they pay you guys not to laugh? I don't feel my body, sounds are compacted" (ketamine day, subject 21). Due to the strict definition of hallucination employed in this study, all perceptual alterations were rated as illusions rather than hallucinations. As a result, there were no significant drug effects on the hallucinatory behavior item of the BPRS. In the RMANOVA performed on the suspiciousness item, ketamine (ketamine by time interaction: $F_{6,132} = 7.8$, $P = 0.004$), but not lorazepam significantly increased scores. The most common paranoid ideation expressed by subjects receiving ketamine was that research staff and others were plotting against them. One subject complained that staff inserted thoughts into his mind (ketamine day, subject no. 6). In the RMANOVA performed on the unusual thought content item, ketamine (ketamine by time interaction: $F_{6,132} = 59.0$, $P = 0.0001$), but not lorazepam significantly increased scores. Illustrating unusual thought content, one subject noted "I feel like a human apple... I feel like a giant pumpkin that's turned human ... I feel like a human computer, like a female on Star Trek" (ketamine day, subject no. 16).

Negative symptoms

Ketamine, and to a lesser extent lorazepam, increased scores on BPRS items associated with the negative symptoms of schizophrenia ($n = 23$, Fig. 1). RMANOVA revealed significant effects of ketamine (ketamine by time interaction: $F_{6,132} = 35.2$, $P = 0.0001$) and lorazepam (lorazepam by time interaction: $F_{6,132} = 7.8$, $P = 0.0001$). No other interactive effects attained significance in the ANOVA. There were no significant differences in baseline scores between test days.

In the RMANOVA performed on blunted affect data, the ketamine by time interaction effects ($F_{6,132} = 13.2$, $P = 0.0001$), lorazepam by time interaction effects ($F_{6,132} = 8.3$, $P = 0.0001$), but not the ketamine by lorazepam by time interaction reached significance. In contrast, a post-hoc RMANOVA revealed that the ketamine-lorazepam produced greater affective blunting than did ketamine (drug by time interaction: $F_{6,132} = 3.2$, $P = 0.02$). In the RMANOVA performed on the motor retardation item, the ketamine by time interaction effects ($F_{6,132} = 17.1$, $P = 0.0001$), lorazepam by time interaction effects ($F_{6,132} = 5.9$, $P = 0.0006$), and ketamine by lorazepam by time interaction ($F_{6,132} = 2.7$, $P = 0.03$) reached significance. Motor retardation produced by lorazepam reflected its sedative-hypnotic effects. However, subjects clearly distinguished ketamine effects from sedation. For example, one subject noted "I feel so distant from everything. I don't feel drowsy. I feel like it [ketamine] is keeping me awake' (ketamine day, subject no. 10). Ketamine also increased emotional withdrawal. The RMANOVA performed on the emotional withdrawal data revealed a significant ketamine by time interaction ($F_{6,132} = 48.0$, $P = 0.0001$), but not significant lorazepam effects.

BPRS activation factor score

The RMANOVA performed on BPRS activation factor scores (Fig. 1) revealed significant ketamine effects (ketamine by time interaction: $F_{6,132} = 25.6$, $P = 0.0001$). Neither lorazepam effects nor the lorazepam-ketamine interaction effects were significant.

BPRS anxious depression factor score

Lorazepam significantly reduced emotional distress associated with ketamine administration (Fig. 1). In the RMANOVA, the effects of ketamine (ketamine by time interaction: $F_{6,132} = 18.5$, $P = 0.0001$); and the ketamine by lorazepam by time interaction ($F_{6,132} = 3.8$, $P = 0.01$) reached significance. Neither the main effect of lorazepam nor the interaction of lorazepam and time was significant. There were no significant baseline differences between test days.

Clinician-Administered Dissociative States Scale (CADSS)

Figure 2 presents the total scores on the CADSS in healthy subjects ($n = 23$). Lorazepam did not significantly reduce the prominent perceptual effects of ketamine. The RMANOVA performed on total CADSS scores revealed significant ketamine effects (ketamine by time interaction: $F_{5,110} = 66.2$, $P = 0.0001$) and a non-significant trend for lorazepam to reduce ketamine-induced perceptual alterations (ketamine by lorazepam by time interaction: $F_{5,110} = 2.6$, $P = 0.1$).

Ketamine increased scores on the five CADSS subscales. The body perception subscale showed significant effects of ketamine effects (ketamine by time interaction: $F_{5,110} = 26.0$, $P = 0.0001$). The most common reported experiences were alterations in the shape or position of limbs. Another common sensation was the

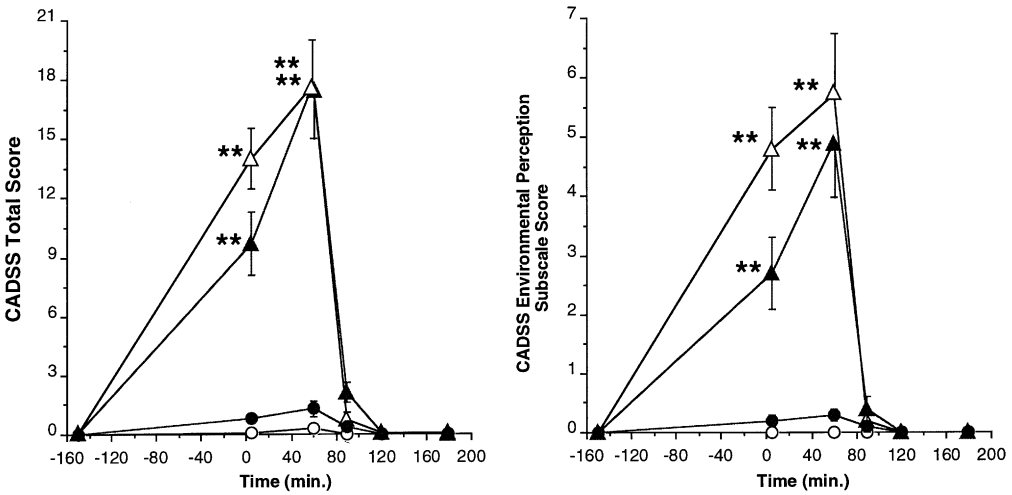

Fig. 2 Ketamine and lorazepam effects on the clinician-administered dissoclative states scale (CADSS) in healthy subjects ($n = 23$). *From left to right*, CADSS total score and environmental perception subscale are presented. Data are presented as mean values ±SEM. Significant increases from baseline by Dunnett's multiple *t*-tests are indicated: $^{**}P < 0.01$. All other statistics are presented in the text. Test days are depicted as follows: (○) placebo, (△) ketamine, (▲) ketamine-lorazepam, and (●) lorazepam

feeling of floating or flying, "everything is going away and away and away ... it feels like I'm flying over the ocean really fast" (ketamine day, subject no. 21).

Results from the environmental perception subscale of the CADSS are presented in Fig. 2. The RMANOVA for the environmental perception subscale showed significant ketamine effects (ketamine by time interaction: $F_{5,110} = 46.8$, $P = 0.0001$). The ANOVA also revealed a trend for lorazepam to reduce ketamine effects (ketamine by lorazepam by time: $F_{5,110} = 2.8$, $P = 0.08$). Ketamine produced perceptual alterations within and across sensory domains. For example, one subject reported, "I feel like I'm on a roller coaster, everything is distorted ... the curtains look like they can reach out and touch me ... the wall seems to be doing a regeneration thing, like rabbits .. the creases in the sheets look like the face of a man ... when she says something, I can immediately see it in my brain" (ketamine-lorazepam day, subject no. 16). Another subject noted, "this machine takes on different shapes. The machine fluffed up around me and then it got very flat. You look like you are dancing under a strobe light ... you went through a few different body shapes, like cartoon figures" (ketamine-lorazepam day, subject no. 9).

Feelings of unreality were also increased by ketamine. The RMANOVA performed on these data showed significant ketamine effects (ketamine by time interaction: $F_{5,110} = 205.2$, $P = 0.0001$). Feelings of unreality produced by ketamine included depersonalization, derealization, and identity-related alterations. Both ketamine and lorazepam worsened the sense of impaired memory and the combination of both drugs was worse than either drug alone. The ANOVA for memory impairment subscale indicated that ketamine effects (ketamine by time interaction: $F_{5,110} = 32.2$, $P = 0.0001$) were significant. There appeared to be a gender-related effect of lorazepam on sense of impaired memory (lorazepam by gender: $F_{1,21} = 4.9$, $P = 0.04$; lorazepam by time by gender: $F_{5,104} = 2.8$, $P = 0.07$; ketamine by lorazepam by time by gender: $F_{5,105} = 3.3$, $P = 0.04$). The data suggested that females (lorazepam by time: $F_{5,35} = 5.7$, $P = 0.004$), but not males, found that lorazepam produced a subjective sense of impaired memory. Time perception was significantly slowed by ketamine (ketamine by time interaction effects: $F_{5,110} = 26.5$, $P = 0.0001$), although lorazepam did not alter this perceptual change.

Measures sensitive to impairments in frontal cortical function

Vigilance

Vigilance data are presented in Table 1. RMANOVA revealed that the number of items correctly identified on the continuous performance test of vigilance was reduced by lorazepam ($F_{1,21} = 16.4$, $P = 0.0006$) and ketamine ($F_{1,21} = 6.7$, $P = 0.02$) in healthy subjects ($n = 22$). However, the drug effects were not interactive. As summarized in Table 1, post-hoc within subjects contrasts revealed that the combination of ketamine and lorazepam reduced the number of correct responses relative to the placebo test day, but the combination did not differ significantly from either the ketamine or lorazepam test days. Similarly, RMANOVA revealed that both ketamine ($F_{1,21} = 6.7$, $P = 0.02$) and lorazepam ($F_{1,21} = 16.4$, $P = 0.0006$) increased the number of errors of omission in a non-interactive fashion. Post-hoc within subjects contrasts found that lorazepam, but not ketamine, increased omission errors relative to placebo. The combination of both medications increased omission errors relative to both placebo and ketamine. The RMANOVAs performed on both commission errors and response latency data were not significant.

Distractibility

As described in Table 1, drug effects on distractibility were in a similar direction, but more pronounced, than

Table 1 The effects of ketamine and lorazepam upon measures sensitive to frontal cortical impairment in healthy subjects[a]

Assessment	Placebo lorazepam placebo ketamine	Placebo lorazepam active ketamine	Active lorazepam active ketamine	Active lorazepam placebo ketamine
Vigilance[b]				
Number correct	28.4 ± 1.3	28.5 ± 0.8¶	24.5 ± 1.4*	27.5 ± 0.6
Omission errors	0.3 ± 0.1	1.5 ± 0.8¶¶	4.2 ± 0.9***	2.5 ± 0.6**¶
Commission errors	0.0 ± 0.0	2.0 ± 1.5*	1.0 ± 0.3	1.1 ± 0.4
Latency	46.8 ± 1.4	46.1 ± 1.6	44.0 ± 2.5	45.9 ± 1.1
Distractibility[c]				
Number correct	28.8 ± 0.3	24.6 ± 1.4***¶¶¶	15.5 ± 2.2***	22.5 ± 1.1***¶¶¶
Omission errors	1.2 ± 0.3	5.3 ± 1.4***¶¶¶	14.5 ± 2.0***	7.5 ± 1.1***¶¶¶
Commission errors	0.4 ± 0.1	1.5 ± 0.5**	2.3 ± 0.8***	0.9 ± 0.2¶¶¶
Latency	44.8 ± 1.4	46.4 ± 1.6¶¶	49.2 ± 2.2***	46.4 ± 1.5¶
Verbal fluency[d]				
Words generated	16.7 ± 1.2	13.4 ± 1.0***	13.8 ± 1.0***	15.7 ± 0.9*¶¶¶
Proverb interpretation[e]				
Concreteness	1.5 ± 0.4	4.9 ± 0.9***¶¶¶	8.8 ± 0.9***	5.0 ± 0.8***¶¶¶
Bizareness	0.9 ± 0.3	1.5 ± 0.3*¶	2.0 ± 0.5***	1.0 ± 0.2¶¶¶
No response	0.0 ± 0.0	1.1 ± 0.4**	0.4 ± 0.2	0.0 ± 0.0
Wisconsin Card Sorting Test[f]				
Perseverative error	22.1 ± 5.5	41.8 ± 10.2$^{$$}$	44.0 ± 6.0$^{$$}$	13.4 ± 2.9§§
% Perseverative error	55.6 ± 5.2	62.4 ± 6.7	62.8 ± 3.8	44.0 ± 4.6§
Non-persev error	13.6 ± 2.1	20.8 ± 5.1$^{$}$	25.0 ± 2.7$^{$$}$	15.8 ± 2.2§
Categories	5.1 ± 0.4	2.6 ± 0.9$^{$$$}$	1.5 ± 0.6$^{$$$}$	5.2 ± 0.5§§§
Trials to 1st category	32.7 ± 6.8	59.9 ± 20.4	88.5 ± 15.3$^{$$$}$	21.4 ± 3.6§§§
Correct cards	72.5 ± 3.8	56.0 ± 7.0	58.8 ± 7.3	79.8 ± 3.9
Loss of set	1.6 ± 0.7	1.0 ± 4.2	1.8 ± 0.4	2.0 ± 0.9

[a]Data presented are mean ± SEM
[b]Based on healthy subjects completing the vigilance task on all 4 test days ($n = 22$)
[c]Based on healthy subjects completing the distractibility task on all 4 test days ($n = 20$)
[d]Based on healthy subjects completing the verbal fluency task on all 4 test days ($n = 23$)
[e]Based on healthy subjects completing the proverb interpretation task on all 4 test days ($n = 23$)
[f]Based on healthy subjects receiving placebo ketamine/placebo lorazepam ($n = 11$), ketamine/placebo lorazepam ($n = 8$), ketamine/lorazepam ($n = 6$), and placebo ketamine/lorazepam ($n = 5$) on their first test day
For comparisons to placebo/placebo by post-hoc within subjects contrasts. *$P < 0.1$; **$P < 0.05$; ***$P < 0.01$
For comparisons to active lorazepam/active ketamine by post-hoc within subjects contrasts. $^{¶}P < 0.1$; $^{¶¶}P < 0.05$; $^{¶¶¶}P < 0.05$
For comparisons to placebo/placebo by post-hoc Fisher's Protected LSD tests: $^{$}P < 0.1$; $^{$$}$P < 0.05; $^{$$$}P < 0.01$
For comparisons to active lorazepam/active ketamine by post-hoc Fisher's protected LSD tests: $^{§}P < 0.1$; $^{§§}P < 0.05$; $^{§§§}P < 0.01$

drug effects on vigilance. RMANOVA revealed that ketamine ($F_{1,19} = 14.7$, $P = 0.001$) and lorazepam ($F_{1,19} = 48.6$, $P = 0.0001$) reduced the number of correct responses in healthy subjects ($n = 20$) on the distractibility task. RMANOVA also revealed a non-significant trend for an interaction of ketamine and lorazepam effects ($F_{1,19} = 2.1$, $P = 0.1$). As described in Table 1, post-hoc within-subjects contrasts revealed that lorazepam and the ketamine-lorazepam combination reduced the number of correct responses relative to placebo. The ketamine-lorazepam combination also reduced the number of correct responses relative to both ketamine and lorazepam test days. Similarly, both ketamine ($F_{1,19} = 14.7$, $P = 0.001$) and lorazepam ($F_{1,19} = 48.6$, $P = 0.0001$) increased omission errors. Post-hoc within subjects contrasts reported in Table 1, found that ketamine, lorazepam, and the ketamine-lorazepam combination increased omission errors relative to placebo. The ketamine-lorazepam combination also increased omission errors relative to the ketamine and lorazepam test days. RMANOVA revealed that ketamine ($F_{1,19} = 4.6$, $P = 0.04$) significantly increased errors of commission, while lorazepam effects were not significant. Post-hoc within-subjects contrasts found that ketamine and the ketamine-lorazepam combination increased commission errors relative to placebo. The ketamine-lorazepam combination also increased commission errors relative to the lorazepam test day. No main effects in the RMANOVA performed upon response latency data reached significance. Post-hoc within subjects contrasts found increased response latency on the ketamine-lorazepam test day relative to the placebo and ketamine test days.

Verbal fluency

Ketamine produced dose-dependent decreases in verbal fluency ($F_{1,22} = 24.5$, $P = 0.0001$). Post-hoc within subjects contrasts (Table 1) revealed that ketamine and the ketamine-lorazepam combination reduced the rate of word generation relative to placebo. The ketamine-

lorazepam combination also reduced the rate of word generation relative to the lorazepam test day.

Proverb interpretation

Three aspects of proverb interpretation were evaluated: concreteness, bizarreness, and failure to respond (Table 1). RMANOVA performed on concreteness data revealed that both ketamine ($F_{1,22} = 27.3$, $P = 0.0001$) and lorazepam ($F_{1,22} = 21.0$, $P = 0.0001$), but not the interactive effects of these drugs were associated with significant effects. Post-hoc within subjects contrasts revealed that both ketamine and lorazepam increased the concreteness of proverb interpretations and that the combined medication effects were significantly greater than either drug given individually. For example, in response to the proverb "let sleeping dogs lie," one subject commented "don't touch Suzy" (his dog), she's not bothering anybody! (ketamine day, subject no. 1), while another subject said "don't wake him up," he'll start barking (ketamine-lorazepam day, subject no. 13).

A RMANOVA performed on bizarreness data indicated that ketamine ($F_{1,22} = 6.0$, $P = 0.02$), but not lorazepam or the ketamine by lorazepam interaction had significant effects. Post-hoc within-subjects contrasts performed on these data (Table 1), revealed that the ketamine-lorazepam test day was associated with a significant increase in the bizarreness of proverb interpretations relative to both the placebo and lorazepam test days. There was also a trend for interpretations on the ketamine-lorazepam test day to be more bizarre than the ketamine test day. Bizarre proverb interpretations on ketamine often reflected thought disorder. For example, in response to "one can ride a free horse to death," a subject responded, "all I can associate with that is what I heard in church once when the priest said going to hell on roller skates in a basket" (ketamine day, subject no. 1). Also, some interpretations were illogical, as illustrated by this interpretation of the proverb "a stream cannot rise higher than its source": "if you beget something, you're never going to grow up to be bigger than you are" (ketamine-lorazepam day, subject no. 9). A RMANOVA performed on data assessing the failure to respond to a proverb with an interpretation of any kind revealed that ketamine ($F_{1,22} = 10.5$, $P = 0.004$), but not lorazepam, significantly increased the failure to respond.

Wisconsin Card Sorting Test (WCST)

Ketamine, but not lorazepam, increased perseverative errors on the WCST. The ANOVA performed on perseverative errors data from the first test day of each subject revealed significant drug effects ($F_{3,26} = 3.6$, $P = 0.03$). Post-hoc Fishers PLSD tests, presented in Table 1, revealed that both ketamine and the ketamine-lorazepam combination increased perseverative errors relative to placebo and lorazepam (ketamine versus lorazepam: $P = 0.02$). The ANOVA performed on percent perseverative error data was not significant. However, post-hoc Fishers PLSD tests indicated that both the ketamine ($P < 0.05$) and ketamine-lorazepam ($P = 0.06$) test days were associated with a greater percentage of perseverative errors than the lorazepam test day. The ANOVA performed upon non-perseverative errors was not significant.

Ketamine, but not lorazepam, reduced the number of categories successfully completed on the WCST. The ANOVA performed on this data revealed a significant drug effect ($F_{3,26} = 7.6$, $P = 0.0009$). Post-hoc Fisher's PLSD tests, reported in Table 1, found that both ketamine and the ketamine-lorazepam test days significantly decreased the number of categories completed relative to placebo and lorazepam (ketamine versus lorazepam: $P = 0.02$). ANOVA performed on the number of trials to completion of the first category data indicated a drug effect ($F_{3,26} = 4.1$, $P = 0.02$). The post-hoc Fisher's PLSD tests performed on these data found that ketamine-lorazepam increased the number of trials relative to the placebo and lorazepam test days. There were no significant drug effects on loss of set.

Learning and memory

Ketamine and lorazepam produced delay-dependent and interactive recall impairments (Fig. 3). In the overall RMANOVA, the main effects of ketamine ($F_{1,22} = 32.1$, $P = 0.0001$), lorazepam ($F_{1,22} = 43.3$, $P = 0.0001$), and the duration of delay between stimulus presentation and testing ($F_{2,44} = 158.0$, $P = 0.0001$) were highly significant. The interactive effects of ketamine and delay ($F_{2,44} = 16.2$, $P = 0.0001$) and lorazepam and delay ($F_{2,44} = 21.6$, $P = 0.0001$) were highly significant. Also, the interactive effects of ketamine, lorazepam, and delay showed a non-significant trend toward significance ($F_{2,44} = 3.0$, $P = 0.06$). In order to examine this trend, the ketamine and ketamine-lorazepam test days were directly compared. This comparison suggested that lorazepam potentiated the amnestic effects of ketamine ($F_{8,176} = 2.8$, $P = 0.02$). Post-hoc RMANOVAs were employed to evaluate the interactive effects of ketamine and lorazepam at each level of delay. Neither ketamine nor lorazepam had significant effects on immediate recall and their interactive effects were not significant. Following a distraction, both ketamine ($F_{1,22} = 38.6$, $P = 0.0001$) and lorazepam ($F_{1,22} = 28.0$, $P = 0.0001$) effects were highly significant, although their interactive effects were not significant. Following a 10-min delay, ketamine effects ($F_{1,22} = 14.1$, $P = 0.001$), lorazepam effects ($F_{1,22} = 50.3$, $P = 0.0001$), and the interaction of ketamine and lorazepam effects ($F_{1,22} = 5.7$, $P = 0.03$) were significant.

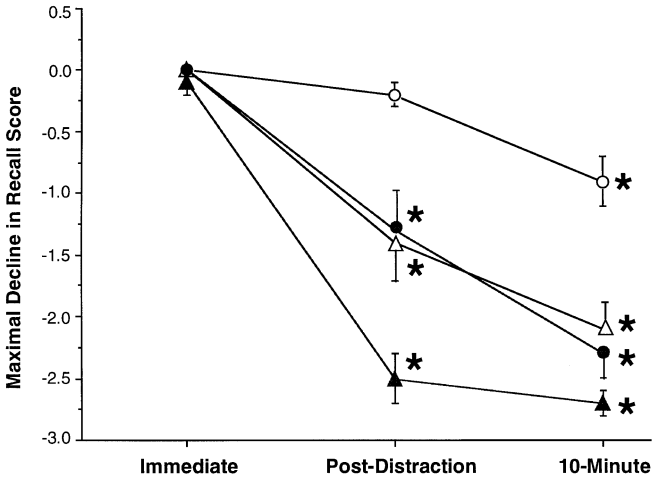

Fig. 3 Ketamine and lorazepam effects on learning and memory as assessed by the recall item of the mini-mental state examination in healthy subjects ($n = 23$). Data are presented as mean values ± SEM for the peak decline in recall score from the pre-drug baseline for each test day. Significant decreases from baseline by Dunnett's multiple *t*-tests are indicated: $*P < 0.01$. All other statistics are presented in the text. Test days are depicted as follows: (○) placebo, (△) ketamine, (▲) ketamine-lorazepam, and (●) lorazepam

Visual analog scales of mood states

Data from the visual analog scales are presented in Fig. 4. Neither ketamine nor lorazepam significantly effected visual analogue scales assessing irritability and sadness.

Anxiety

Ketamine increased self-rated anxiety and lorazepam did not significantly block this effect. The RMANOVA performed on anxiety data found a significant ketamine by time interaction ($F_{6,126} = 8.2$, $P = 0.0001$).

Drowsiness

Lorazepam increased self-reported drowsiness to a greater extent than ketamine and the combination of these medications potentiated the effects of either drug administered individually. In the RMANOVA, lorazepam (lorazepam by time interaction: $F_{6,126} = 6.2$, $P = 0.0001$), ketamine (ketamine by time interaction: $F_{6,126} = 2.5$, $P = 0.04$), and the interactive effects of ketamine, lorazepam, and time ($F_{6,126} = 2.4$, $P = 0.05$) were significant.

High

Ketamine (ketamine by time interaction: $F_{6,126} = 29.2$, $P = 0.0001$), but not lorazepam, produced a subjective sense of being high. One subject described the high as ethanol-like "like when I'm drinking, but I'm hazier than when I'm drinking" (subject no. 6).

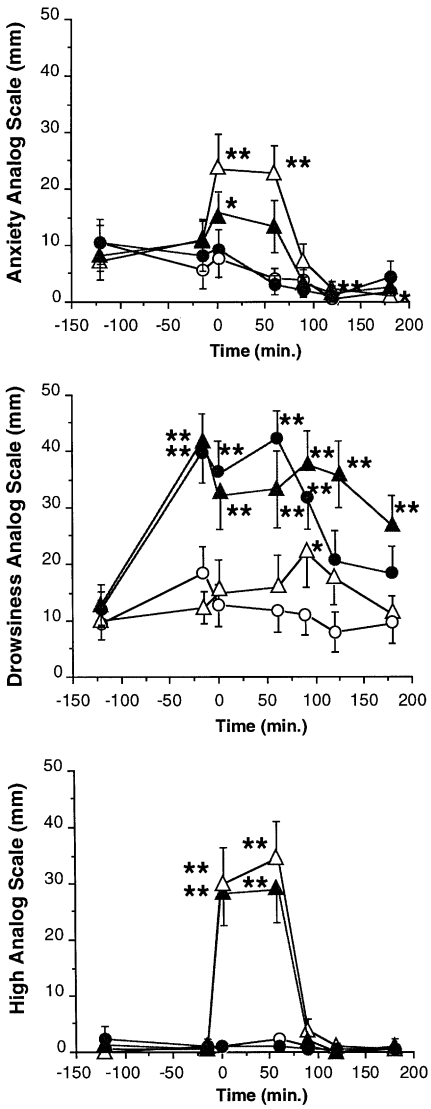

Fig. 4 Ketamine and lorazepam on visual analog scales of mood states in healthy subjects ($n = 23$), *from top to bottom*, anxiety, drowsiness, and high. Data are presented as mean values ± SEM. Significant increases from baseline by Dunnett's multiple *t*-tests are indicated: $*P < 0.05$; $**P < 0.01$. All other statistics are presented in the text. Test days are depicted as follows: (○) placebo, (△) ketamine, (▲) ketamine-lorazepam, and (●) lorazepam

Neuroendocrine measures

Cortisol

Ketamine (ketamine by time interaction: $F_{3,66} = 55.4$, $P = 0.0001$) increased cortisol levels and there was a trend for lorazepam (lorazepam by time interaction: $F_{3,66} = 3.4$, $P = 0.06$) to have a similar effect (Fig. 5). In order to evaluate the possibility that stress related to emesis increased cortisol levels, the RMANOVA was

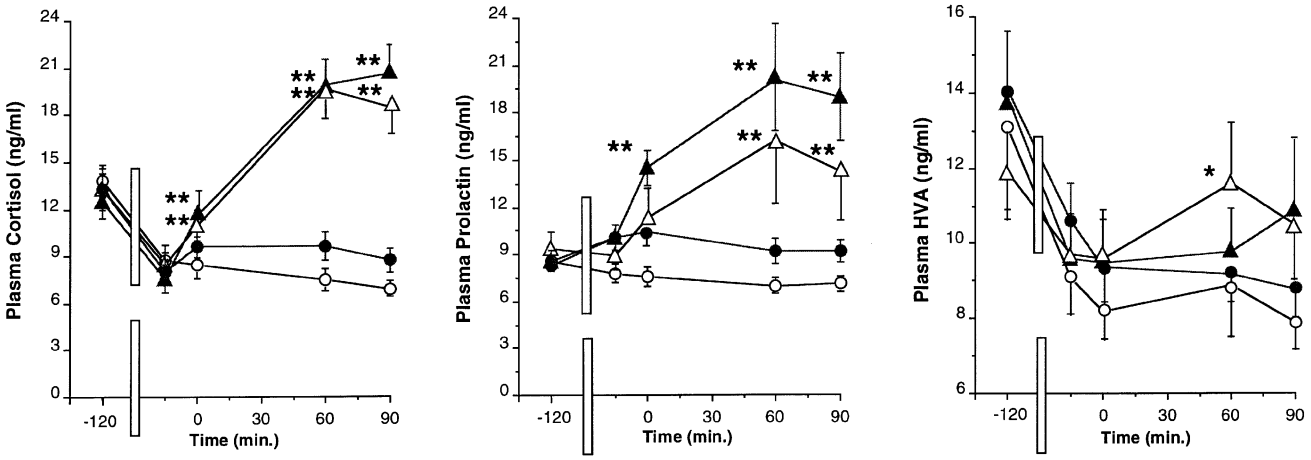

Fig. 5 Ketamine and lorazepam effects on neuroendocrine indices, *from left to right*, cortisol (n =23), prolactin (n =21), and homovanillic acid (*HVA*; n =23) in healthy subjects. Data are presented as mean values ± SEM. Significant changes from baseline (prolactin) or–15 min (cortisol, HVA) timepoint by Dunnett's multiple t-tests are indicated: $^*P < 0.05$; $^{**}P < 0.01$. All other statistics are presented in the text. Test days are deplicted as follows: (○) placebo, (△) ketamine, (▲) ketamine-lorazepam, and (●) lorazepam

repeated adding emesis as a between-subjects factor. This analysis revealed that emesis was associated with greater cortisol increases (emesis: $F_{1,22} = 9.4$, $P = 0.006$; ketamine by time by emesis: $F_{3,63} = 13.1$, $P = 0.0002$).

Prolactin

Ketamine (ketamine by time interaction: $F_{4,80} = 9.3$, $P = 0.004$), and to a lesser extent lorazepam (lorazepam by time interaction: $F_{4,80} = 3.6$, $P = 0.03$), increased prolactin levels (Fig. 5). There also was a gender effect related to lorazepam (lorazepam by time by gender: $F_{4,76} = 4.0$, $P = 0.03$; ketamine by lorazepam by time by gender: $F_{4,76} = 2.5$, $P = 0.09$). A post-hoc RMANOVA also indicated that the prolactin response was greater on the ketamine-lorazepam test day than on the ketamine test day and that peak prolactin levels were higher in females than males (ketamine, lorazepam, time, and gender effects: $F_{4,80} = 3.3$, $P = 0.04$). When data from all test days were analyzed separately by gender, ketamine and lorazepam effects remained significant for males ($n = 15$, ketamine by time: $F_{4,52} = 9.4$, $P = 0.0003$; lorazepam by time: $F_{4,52} = 6.7$, $P = 0.002$), but not females ($n = 8$, ketamine by time: $F_{4,24} = 4.2$, $P = 0.07$; lorazepam by time: $F_{4,24} = 2.3$, $P = 0.1$). The presence or absence of emesis also was added as a between-subjects factor in the analysis. Emesis was associated with increased prolactin responses to ketamine and there was a similar trend for lorazepam (ketamine by time by emesis: $F_{4,76} = 4.7$, $P = 0.03$; lorazepam by time by emesis: $F_{4,76} = 2.7$, $P = 0.07$; ketamine by lorazepam by time by emesis: $F_{4,76} = 2.3$, $P = 0.1$).

HVA

As presented in Fig. 5, ketamine and lorazepam blunted a test day decline in plasma HVA in healthy subjects ($n = 23$). The RMANOVA performed on HVA data revealed significant effects of time ($F_{4,88} = 13.7$, $P = 0.0003$), the ketamine by time interaction ($F_{4,88} = 3.9$, $P = 0.02$) and the lorazepam by time interaction ($F_{4,88} = 2.8$, $P = 0.05$). No other effects were significant in the ANOVA. The addition of emesis and gender to the analysis did not effect results. A post-hoc RMANOVA comparing the ketamine and ketamine-lorazepam test days suggested that lorazepam blocked a ketamine-induced increase in HVA levels ($F_{4,88} = 3.3$, $P = 0.02$).

Plasma lorazepam and ketamine levels

Ketamine and lorazepam did not show evidence of a pharmacokinetic interaction in this study and there were no significant changes detected in blood levels of either drug during the assessment period (Fig. 6). The RMANOVA performed on lorazepam levels comparing the lorazepam and ketamine-lorazepam test days found a significant time effect ($F_{1,20} = 17.1$, $P = 0.0001$). No other main effect or interaction was significant in this analysis. Also, there were no significant gender-related differences in lorazepam blood levels and lorazepam did not significantly modulate ketamine levels. Similarly, the RMANOVA comparing the ketamine and the ketamine-lorazepam test days indicated a significant time effect ($F_{2,12} = 16.7$, $P = 0.0003$), but no other significant main effects or interactions.

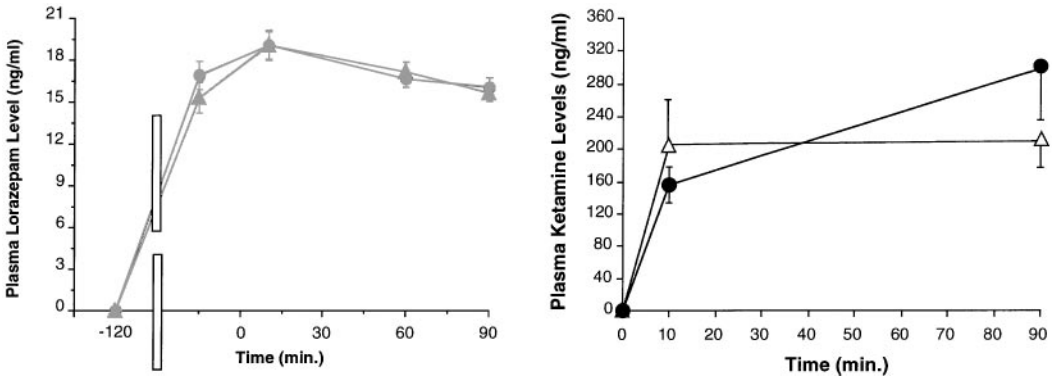

Fig. 6 Interactive pharmacokinetic effects of ketamine and lorazepam. The *left figure* depicts the effects of ketamine on plasma lorazepam levels in healthy subjects ($n = 21$). The *right figure* depicts lorazepam effects on plasma ketamine levels in healthy subjucts ($n = 7$) Data are presented as mean values ± SEM. Statistical analyses are presented in the text. Test days are depicted as follows: (△) ketamine, (▲) ketamine-lorazepam, and (●) lorazepam

Vital signs

Blood pressure

Ketamine increased systolic blood pressure in healthy subjects ($n = 20$; Fig. 7). The RMANOVA revealed significant effects of ketamine (ketamine by time interaction: $F_{6,114} = 10.4$, $P = 0.0001$) and the ketamine by lorazepam interaction ($F_{1,19} = 14.5$, $P = 0.001$). Post-hoc within subjects Dunnett's *t*-tests revealed significant increases from baseline ($P < 0.01$) on both the ketamine and ketamine-lorazepam test days. Ketamine increased diastolic blood pressure in healthy subjects ($n = 21$; Fig. 7). The RMANOVA revealed significant ketamine effects (ketamine by time interaction: $F_{6,120} = 9.9$, $P = 0.0001$).

Pulse

Ketamine also increased pulse rate in healthy subjects ($n = 22$; Fig. 7). The RMANOVA revealed significant ketamine (ketamine by time interaction ($F_{6,126} = 7.8$, $P = 0.0001$) and lorazepam (lorazepam by time interaction: $F_{6,126} = 3.1$, $P = 0.007$) effects.

Respiratory rate

Neither ketamine nor lorazepam had significant effects on respiratory rate. Baseline and peak increases in respiratory rate (respirations/min) for each test day were as follows: placebo: 18.6 ± 0.4 baseline, 1.4 ± 0.5 peak increase; ketamine: 18.9 ± 0.4 baseline, 1.3 ± 0.5 peak increase; ketamine-lorazepam: 18.7 ± 0.5 baseline, 1.2 ± 0.6 peak increase; lorazepam: 18.2 ± 0.5 baseline, 2.7 ± 0.6 peak increase.

Other responses

Motor function

Neither ketamine nor lorazepam affected the rate of finger-tapping with the dominant hand ($n = 17$; placebo: 53.7 ± 1.4 taps; ketamine: 51.7 ± 2.1 taps; ketamine-lorazepam: 52.6 ± 1.4 taps; lorazepam: 54.3 ± 1.0 taps; ANOVA, ketamine: $F_{1,16} = 2.2$, $P = 0.2$; lorazepam: $F_{1,16} = 0.6$, $P = 0.4$). Lorazepam increased the rate of finger-tapping using the non-dominant hand, while ketamine effects showed a trend in the opposite direction, although their effects were not interactive ($n = 14$; placebo: 49.7 ± 1.5 taps; ketamine: 47.2 ± 1.7 taps; ketamine-lorazepam: 50.2 ± 1.4 taps; lorazepam: 51.4 ± 1.3 taps; ANOVA, ketamine: $F_{1,13} = 4.1$, $P = 0.07$; lorazepam: $F_{1,13} = 5.5$, $P = 0.04$).

Nystagmus

Fifteen subjects had nystagmus after receiving ketamine and the combination of ketamine and lorazepam; two subjects had nystagmus on ketamine, but not on ketamine-lorazepam; three subjects had nystagmus on ketamine-lorazepam, but not ketamine; and ten subjects did not have nystagmus during testing.

Emesis

Four subjects vomited after receiving ketamine and the combination of ketamine and lorazepam; six subjects vomited after receiving ketamine, but not on ketamine-lorazepam; one subject vomited following administration of ketamine and lorazepam, but not ketamine alone; and 19 subjects did not suffer incidents of emesis during testing.

Safety issues

On follow-up interview, no subject had lingering or recurrent physiological or psychological effects such as nightmares or flashbacks. A few subjects noted reduced sleep quality on the evenings of ketamine test days and reduced energy or concentration on the following day.

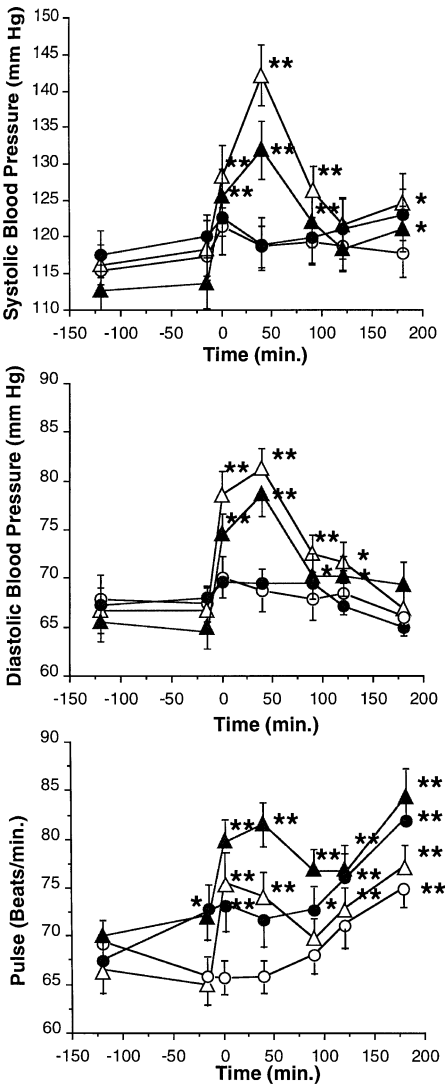

Fig. 7 Ketamine and lorazepam effects on systolic blood pressure ($n = 23$), diastolic blood pressure ($n = 22$), and pulse ($n = 23$) in healthy subjects (presented respectively, *top to bottom*). Data are presented as mean values ± SEM. Significant increases from baseline by Dunnett's multiple *t*-tests are indicated: $*P < 0.05$; $**P < 0.01$. All other statistics are presented in the text. Test days are depicted as follows: (○) placebo, (△) ketamine, (▲) ketamine-lorazepam, and (●) lorazepam

Discussion

This study extended previous research in healthy humans indicating that ketamine effects are not isomorphic to any known psychiatric illness. However, the data continue to suggest similarity of many ketamine effects to symptoms and cognitive deficits associated with schizophrenia and dissociative states (Domino et al. 1965; Ghoneim et al. 1985; Øye et al. 1992; Krystal et al. 1994; Malhotra et al. 1996). Ketamine produced positive symptoms associated with schizophrenia including paranoid and grandiose delusions, thought disorder, and illusions. Hallucinations, strictly defined as internally generated sensory experiences devoid of a sensory referent, were not produced by ketamine in this study. Ketamine produced negative symptoms, including blunted emotional responsivity, psychomotor retardation, and emotional withdrawal. It also produced perceptual alterations associated with dissociative states, including distorted sensory perceptions, altered body perception, feelings of unreality, slowing of time, and a sense of impaired memory. Ketamine impaired cognitive functions including delayed recall and performance on tests sensitive to frontal cortical impairment, without slowing finger-tapping. Mood effects of ketamine included activation, anxiety, and high. Ketamine also increased plasma cortisol and prolactin levels and blunted a test day decline in plasma HVA.

Consistent with previous reports (File et al. 1982; Roache and Griffiths 1987; File 1992; Rush et al. 1993), lorazepam reduced vigilance and increased distractibility, increasing omission rather than commission errors. It also reduced the capacity to interpret proverbs abstractly, without increasing the tendency to give bizarre responses. Lorazepam did not significantly reduce verbal fluency or impair performance on the WCST. However, it produced a delay-dependent recall impairment in all subjects and a sense of impaired memory in females. Lorazepam had modest stimulatory effects on plasma HVA, prolactin, and cortisol levels, contrasting with previous reports of inhibitory benzodiazepine effects (Grandison 1983; Tuomisto and Mannisto 1985; Charney et al. 1986; Nutt and Cowen 1987). The cause of the discrepancy between the earlier reports and the current study is not clear.

At the dose studied, lorazepam failed to block many undesirable ketamine effects. Further, these drugs showed a range of interactions from antagonism to potentiation. Subhypnotic lorazepam reduced emotional distress and it tended to reduce distorted sensory perceptions associated with ketamine infusion. It also reduced the inability to produce a proverb interpretation, perhaps an indication of reduced thought blocking. However, it failed significantly to block psychotogenic, perceptual, cognitive, neuroendocrine and physiologic ketamine responses. Ketamine sedative effects were intensified by lorazepam. Lorazepam also potentiated ketamine amnestic actions, consistent with previous reports (Freuchen et al. 1976; Tobin 1982). The current data suggested that the capacity of lorazepam to reduce emotional distress and to impair recall of disturbing ketamine effects contributes to its established ability to improve ketamine anesthesia tolerability (Coppel et al. 1973; Fragen and Caldwell 1976; Kothary and Zsigmond 1977; Lilburn et al. 1978; Tucker et al. 1984).

The absence of pharmacokinetic interactions is a strength of the ketamine-lorazepam combination. By potentiating sedative effects, lorazepam permits the use of lower ketamine doses for anesthesia (Freuchen et al. 1976; Idvall et al. 1983). The apparent absence of pharmacokinetic interactions between ketamine and

lorazepam suggests that the potentiation of ketamine sedation is mediated pharmacologically. In contrast, diazepam increases ketamine blood levels due to overlapping involvement of hepatic enzymes (Idvall et al. 1983).

Previous human studies of NMDA antagonists provided evidence of ethanol-like effects (Luby et al. 1959; Krystal et al., in press). Similarly, the current study reported that ketamine produced a drug "high". This euphoria was not produced by lorazepam nor did lorazepam significantly modulate the ketamine high. Unfortunately, this study did not assess whether lorazepam altered the discriminative properties of the ketamine high. This information would have been interesting in light of evidence that ethanol possesses both NMDA antagonist and $GABA_A$ facilitating effects (Suzdak et al. 1986; Lovinger et al. 1989).

Lorazepam and ketamine-induced psychosis

The current data highlight challenges in studying contributions of reduced $GABA_A$ receptor function to the ketamine psychosis (Olney and Farber 1995). GABAergic and glutamatergic systems are integral to cortico-striato-thalamic circuitry implicated in psychosis (Carlsson and Carlsson 1990; Grace 1991). A growing body of research suggests that NMDA receptor stimulation activates GABAergic neurons (White 1989; Agmon and O'Dowd 1992). NMDA antagonists reduce GABAergic inhibition in the cortex (Dingledine et al. 1986) and the septum (Giovanni et al. 1994). In addition, benzodiazepine pretreatment reduces NMDA antagonist stimulation of frontal cortical dopamine turnover (Bowers and Hoffman 1989; Bowers and Morton 1992) and cortical metabolism (Oguchi et al. 1982; Åkeson et al. 1993). They also weakly inhibit NMDA antagonist neurotoxicity (Olney et al. 1991; Olney and Farber 1995). However, other data question the significance of subanesthetic ketamine effects on GABA function. For example, subanesthetic doses of NMDA antagonists have modest effects on GABA synthesis and metabolism (Leonard and Tonge 1970; Manor et al. 1995), may reduce GABA reuptake (Wood and Hertz 1980), and they maintain extracellular GABA levels in the frontal cortex (Moghaddam, personal communication).

The current study is limited in its capacity to evaluate GABAergic modulation of ketamine psychosis. Lorazepam doses that produce anxiolysis, amnesis, and sedation were not effective in preventing ketamine psychosis. However, the anesthesia literature suggests that the IV administration of lorazepam at a higher dose than employed in the current study, 4 mg, reduces ketamine psychosis (Dundee et al. 1977). At this lorazepam dose, sedative effects interfere with prospective behavioral assessments and amnestic effects could interfere with retrospective self-reports. Future studies should examine multiple lorazepam doses, perhaps with IV infusion, as well as multiple ketamine doses to examine further lorazepam-ketamine interactions.

Ketamine, lorazepam, and dissociative states

The capacity of ketamine to elicit sensory and identity-related perceptual distortions in healthy individuals provided further evidence that deficits in NMDA receptor function might contribute to the genesis of dissociative states (Krystal et al. 1994). Ketamine actions in networks modulating sensory association cortex (Corrsen and Domino 1966) and sensory filtering functions of the thalamus have been implicated in ketamine-induced perceptual alterations (Krystal et al. 1995). There was a trend for lorazepam to reduce alterations in sensory perception. However, other dissociative symptoms were not reduced by lorazepam. The limited efficacy of subhypnotic lorazepam to prevent perceptual alterations in the current study may be consistent with the important, but limited, efficacy of benzodiazepines in the treatment of dissociative states (Kluft 1987). Dissociative disorders produce significant suffering and disability, but are without established efficacious pharmacotherapies (Kluft 1987). The current findings support further investigation of glutamatergic models in developing novel pharmacotherapies for dissociative disorders.

Ketamine, lorazepam, and frontal cortical functions

This study replicated and extended earlier findings (Krystal et al. 1994) suggesting that ketamine impairs functions associated with the frontal cortex. This study and others (Krystal et al. 1994) suggest that performance on the Mini-Mental State Examination, fingertapping, and aspects of attention are preserved during subanesthetic ketamine administration. However, ketamine effects cannot be said to be selective for functions associated with the frontal cortex. As NMDA receptors are widely distributed in the brain (Kornhuber et al. 1989), ketamine effects on tests sensitive to frontal cortical impairment could arise from ketamine actions within the frontal cortex or at extrinsic modulatory sites. Further, ketamine appears to modulate a broad spectrum of cognitive functions.

Comparisons of ketamine and lorazepam effects highlighted the prominence of ketamine effects of tasks associated with the frontal cortex. Both ketamine and lorazepam increased omission errors on the vigilance and distractibility tasks without increasing response latency. They also produced comparable levels of concreteness during proverb interpretation. However, ketamine, but not lorazepam, increased commission errors on the continuous performance tasks, reduced verbal fluency, produced bizarre proverb interpretations, and impaired WCST performance. While

these ketamine effects could be ascribed to the frontal cortex, they may also reflect dysfunction in temporoparietal regions involved in interpretive functions (Wise, et al. 1991) or dysregulation of anterior cingulate gyrus activity implicated in the allocation of attention (Pardo et al. 1990; Lahti et al. 1995; McCarthy et al. 1996).

The current data also highlight the complexity of the WCST as a measure of executive functions. Lorazepam-induced attention impairments and concreteness in proverb interpretation were not associated with increased perseverative errors or reduced categories completed on the WCST. Thus, the WCST may be completed using strategies that do not require a high degree of abstract reasoning as long as other cortical functions remain intact. In contrast, the associative aspects of abstract cognition impaired by ketamine appear to be more directly related to the planning, problem-solving, mental set-shifting, and feedback-integrating functions evaluated by the WCST.

Ketamine-induced impairments in frontal cortical function were previously linked to BPRS negative symptoms in healthy subjects (Krystal et al. 1994). Negative symptoms have been previously described in patients with frontal cortical injury (Stuss and Benson, 1986) or schizophrenia (Wolkin et al. 1992). Benzodiazepines may be helpful as an adjunctive pharmacotherapy in the treatment of negative symptoms in schizophrenics (cf. Wolkowitz and Pickar 1991). However, lorazepam increased ketamine-induced negative symptoms and did not improve performance on frontal cortical tasks. In the current study, interactive drug sedative effects were evident on the attention tasks. These sedative effects confound the interpretation of the negative symptom data.

NMDA antagonist effects in humans are of significant interest because of their potential relevance to psychosis, dissociation, substance abuse, and cognitive function. In the current study, lorazepam modulated many ketamine effects, emphasizing the importance of GABA-glutamate interactions in the brain. Further, the current study does not rule out the possibility that higher lorazepam doses might reduce ketamine-induced psychosis. However, the failure of lorazepam to block the ketamine psychosis in the current study highlights limitations of the current knowledge base. Novel pharmacologic approaches should be similarly explored to determine whether they provide a more effective antagonism of ketamine-induced psychosis and thought disorder.

Acknowledgements The authors thank Jonathan White, M.A., Pedro Mendia, M.S., and the staff of the Neurobiological Studies Unit at the West Haven VA Medical Center for their critical contributions to the successful completion of this study. The authors also thank Thomas Cooper, M.A. for his support of the plasma lorazepam level analyses. This study was supported by funding from the Department of Veterans Affairs through the Schizophrenia Biological Research Center (D. Charney, B.S. Bunney) and VA-Yale Alcoholism Research Center (J. Krystal, B. Rounsaville), West Haven, Conn., and by a Merit Review Grant from the Department of Veterans Affairs (J. Krystal). Additional funding care from research grant MH-30929 (D. Cohen, M. Bowers) and MH44866 (P. Goldman-Rakic) from the National Institute of Mental Health, Bethesda, Md.

References

Agmon A, O'Dowd DK (1992) NMDA receptor-mediated currents are prominent in the thalamocortical synaptic response before maturation of inhibition. J Neurophysiol 68:345–349

Åkeson J, Björkman S, Messeter K, Rosén I (1993) Low-dose midazolam antagonizes cerebral metabolic stimulation by ketamine in the pig. Acta Anesthesiol Scand 37:525–531

American Psychiatric Association (1987) Diagnostic and Statistical Manual of Mental Disorders 3rd edn, revised. American Psychiatric Association, Washington, DC

Anis NA, Berry SC, Burton NR, Lodge D (1983) The dissociative anaesthetics, ketamine and phencyclidine, selectively decrease excitation of central neurons by *N*-methyl-D-aspartate. Br J Pharmacol 83:179–185

Bacopoulos NG, Redmond DE, Roth RH (1979) Serotonin and dopamine metabolites in brain regions and cerebrospinal fluid of a primate species: effects of ketamine and fluphenazine. J Neurochem 32:1215–1218

Bell MD, Billington RJ, Becker BR (1985) A scale for the assessment of reality testing: reliability, validity and factorial invariance. J Clin Psychol 53:506–511

Benton AL (1968) Differential behavioral effects in frontal lobe disease. Neuropsychologia 6:53–60

Borkowski JG, Benton AL, Spreen O (1967) Word fluency and brain damage. Neuropsychologia 5:135–140

Bovill JG, Clarke RSJ, Dundee JW, Pandit SK, Moore J (1971) Effect of premedicants and supplements on ketamine anaesthesia. Br J Anesth 43:600–608

Bowers MB Jr, Hoffman FJ Jr (1989) Effects of diazepam on regional brain homovanillic acid following phencyclidine or Δ^9-tetrahydrocannabinol. Biochem Pharmacol 38:2385–2387

Bowers MB Jr, Morton JB (1992) Diazepam antagonizes effects on dopamine metabolism produced by PCP receptor agonists. Prog Neuro-Psychopharmacol Biol Psychiatry 16:211–215

Bowers MB, Heninger GR, Sternberg D, Meltzer HY (1980) Clinical processes and central dopaminergic activity in psychotic disorders. Commun Psychopharmacol 4:177–188

Bresink I, Danysz W, Parson CG, Mutschler E (1995) Different binding affinities of NMDA receptor channel blockers in various brain regions-indication of NMDA receptor heterogeneity. Neuropharmacology 34:533–540

Buchanan RW, Heinrichs DW (1989) The neurological evaluation scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. Psychiatry Res 27:335–350

Byrd LD (1987) Effects of phencyclidine and ketamine on cardiovascular activity and temperature in the squirrel monkey. Life Sci 41:7–13

Carlsson M, Carlsson A (1990) Interactions between glutamatergic and monoaminergic systems within the basal ganglia – implications for schizophrenia and Parkinson's disease. Trend Neurosci 13:272–276

Cartwright PD, Pingel SM (1984) Midazolam and diazepam in ketamine anesthesia. Anesthesia 39:439–442

Chapman LJ, Chapman JP, Miller EN (1982) Reliabilities and intercorrelations of eight measures of proneness to psychosis. J Consult Clin Psychol 50:187–195

Charney DS, Breier A, Jatlow PI, Heninger GR (1986) Behavioral, biochemical, and blood pressure responses to alprazolam in healthy subjects: interactions with yohimbine. Psychopharmacology 88:133–140

Charney DS, Woods SW, Goodman WK, Heninger GR (1987) Serotonin function in anxiety. II: effects of the serotonin agonist MCPP in panic disorder patients and healthy subjects. Psychopharmacology 92:14–24

Collier BB (1972) Ketamine and the conscious mind. Anaesthesia 27:120–134
Coppel DL, Bovill JG, Dunndee JW (1973) The taming of ketamine. Anaesthesia 28:293–296
Corssen G, Domino EF (1966) Dissociative anesthesia: further pharmacologic studies and first clinical experience with phencyclidine derivative CI-581. Anesth Analg 45:29–40
Deutsch SI, Mastropaolo J, Schwartz BL, Rosse RB, Morihisa JM (1989) A "glutamatergic hypothesis" of schizophrenia: Rationale for pharmacotherapy with glycine. Clin Neuropharmacol 12:1–13
Dingledine R, Hynes MA, King GL (1986) Involvement of N-methyl-D-aspartate receptors in epileptiform bursting in the rat hippocampal slice. J Physiol 380:175–189
Domino EF, Chodoff P, Corssen G (1965) Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. Clin Pharm Ther 6:279–291
Dundee JW, Lilburn JK (1978) Ketamine-lorazepam: attenuation of psychic sequelae of ketamine by lorazepam. Anaesthesia 33: 312–314
Dundee JW, Lilburn JK, Nair SG, George KA (1977) Studies of drugs given before anaesthesia. XXVI: Lorazepam. Br J Anesthesia 49:1047–1056
Dundee JW, McGowan WAW, Lilburn JK, McKay AC, Hegarty JE (1979) Comparison of the actions of diazepam and lorazepam. Br J Anaesth 51:439–446
File SE (1992) Effects of lorazepam on psychomotor performance: a comparison of independent-groups and repeated-measures designs. Pharmacol Biochem Behav 42:761–764
File SE, Bond AJ, Lister RG (1982) Interaction between effects of caffeine and lorazepam in performance tests and self-ratings. J Clin Psychopharmacol 2:102–106
Fragen RJ, Caldwell N (1976) Lorazepam premedication – lack of recall and relief of anxiety. Anesth Analg 55:792–796
Freuchen I, Ostergaard J, Kuhl JB, Mikkelsen BO (1976) Reduction of psychotomimetic side effects of Ketalar (ketamine) by Rohypnol (flunitrazepam). A randomized double-blind trial. Acta Anesthesiol Scand 20:97–103
Ghoneim MM, Hinrichs JV, Mewaldt SP (1984) Dose-response analysis of the behavioral effects of diazepam. I. Learning and memory. Psychopharmacology 82:291–295
Ghoneim MM, Hinrichs JV, Mewaldt SP, Petersen RC (1985) Ketamine: behavioral effects of subanesthetic doses. J Clin Psychopharmacol 5:70–77
Giovanni MG, Mutolo D, Bianchi L, Michelassi A, Pepeu G (1994) NMDA receptor antagonists decrease GABA outflow from the septum and increase acetylcholine outflow from the hippocampus: a microdialysis study. J Neurosci 14:1358–1365
Goldstein K (1949) Frontal lobotomy and impairment of abstract attitude. J Nerv Ment Dis 110:93–111
Gordon M (1983) The Gordon diagnostic system. Gordon Systems, DeWitt, N.Y.
Gorham DR (1956) A proverbs test for clinical and experimental use. Psychol Rep 2:1–12
Grace AA (1991) Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience 41:1–24
Grandison L (1983) Actions of benzodiazepines on the neuroendocrine system. Neuropharmacology 22:1505–1510
Hampton RY, Medzihradsky F, Woods JH, Dahlstrom PJ (1982) Stereospecific binding of ^{3}H-phencyclidine in brain membranes. Life Sci 30:2147–2154
Hedlund JL, Vieweg BW (1980) The Brief Psychiatric Rating Scale (BPRS): a comprehensive review. J Operational Psychiatry 11: 48–64
Idvall J, Aronsen KF, Stenberg P, Paalzow L (1983) Pharmacodynamic and pharmacokinetic interactions between ketamine and diazepam. Eur J Clin Pharmacol 24:337–343
Javitt DC, Zukin SR (1991) Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 148:1301–1308
Kane J, Honigfeld G, Singer J, Meltzer H, the Clozapine Collaborative Study Group (1988) Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 45:789–796
Kim JS, Kornhuber HH, Schmid-Burgk W, Holzmüller B (1980) Low cerebrospinal fluid glutamate in schizophrenic patients and a new hypothesis on schizophrenia. Neurosci Lett 20: 379–382
Kluft RF (1987) An update on multiple personality disorder. Hosp Commun Psychiatry 38:363–373
Knox JW, Bovill JG, Clarke RSJ, Dundee JW (1970) Clinical studies of induction agents. XXXVI: Ketamine. Br J Anaesth 42:875–885
Kornhuber J, Mack-Burkhardt F, Riederer P (1989) Regional distribution of [^{3}H]MK-801 binding sites in the human brain. Brain Res 489:397–399
Kothary SP, Zsigmond EK (1977) A double-blind study of the effective antihallucinatory doses of diazepam prior to ketamine anesthesia. Clin Pharmacol Ther 21:108–109
Krystal JH, Seibyl JP, Price LH, Woods SW, Heninger GR, Aghajanian GK, Charney DS (1993) *m*-Chlorophenylpiperazine (MCPP) effects in neuroleptic-free schizophrenic patients: evidence implicating serotonergic systems in the positive symptoms of schizophrenia. Arch Gen Psychiatry 50: 624–635
Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans: psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51:199–214
Krystal JH, Bennett A, Bremner JD, Southwick SM, Charney DS (1995) Toward a cognitive neuroscience of dissociation and altered memory functions in post-traumatic stress disorder. In: Friedman MJ, Charney DS, Deutch AY (eds) Neurobiological and clinical consequences of stress: from normal adaptation to PTSD. Raven Press, New York, N.Y., pp 239–269
Krystal JH, Petrakis IL, Webb E, Cooney NL, Kerper LP, Namanworth S, Trevisan LA, Charney DS (1998) Dose-related ethanol-like effects of the NMDA antagonist, ketamine, in recently detoxified alcoholics. Arch Gen Psychiatry (in press)
Kucera H, Francis WN (1967) Computational analysis of present day American English. Brown University Press, Providence, R.I.
Lahti AC, Holcomb HH, Medoff DR, Tamminga CA (1995) Ketamine activates psychosis and alters limbic blood flow in schizophrenia. Neuroreport 6:869–872
Leonard BE, Tonge SR (1970) Some effects of a hallucinogenic drug (phencyclidine) on neurohumoral substances. Life Sci 9: 1141–1152
Lilburn JK, Dundee JW, Nair SG, Fee JP, Johnston HM (1978) Ketamine sequelae. Evaluation of the ability of various premedicants to attenuate its psychic actions. Anesthesialogy 33:307–311
Loh L, Singer L, Morgan M, Moore PH (1972) Influence of diazepam on the emergence reactions following ketamine anesthesia. Can Anaesth Soc J 19:421–425
Lovinger DM, White G, Weight FF (1989) Ethanol inhibits NMDA-activated ion currents in hippocampal neurons. Science 243:1721–1724
Luby ED, Cohen BD, Rosenbaum G, Gottlieb JS, Kelley R (1959) Study of a new schizophrenomimetic drug-sernyl. AMA Arch Neurol Psychiatry 81:363–369
Malhotra AK, Pinals DA, Weingartner H, Sirocco K, Missar CD, Pickar D, Breier A (1996) NMDA receptor function and human cognition: the effects of ketamine in healthy subjects. Neuropsychopharmacology 14:301–308
Manor D, Behar K, Rothman D, Mason G, Hooten M, Krystal J (1995) Ketamine effects on cortical tricarboxylic acid (TCA) cycle rates and GABA metabolism in rats assessed using magnetic resonance spectroscopy. Presented to the American College of Neuropsychopharmacology 34th Annual Meeting. San Juan, PR, Dec 11–15, p 183

McCarthy G, Puce A, Constable RT, Krystal JH, Gore JC, Goldman-Rakic P (1996) Activation of human prefrontal cortex during spatial and object working memory tasks measured by functional MRI. Cereb Cortex 6: 600–611

Migály P, Károvitz J, Jakab T, Gaál K (1991) Effects of ketamine anesthesia and stress-reducing psychological methods on surgery patients. In: Spielberger CD, Sarason IG, Kulcsár Z, Van Heck GL (eds) Stress and emotion: anxiety, anger, and curiosity. Hemisphere Publishing, New York, 14:215–224

Milner B (1964) Some effects of frontal lobectomy in man. In: Warren JM, Akert K (eds) The frontal granular cortex and behavior. McGraw-Hill, New York, pp 313–334

Nutt DJ, Cowen PJ (1987) Diazepam alters brain 5-HT function in man: implications for the acute and chronic effects of benzodiazepines. Psychol Med 17:601–607

Oguchi K, Arakawa K, Nelson SR, Samson F (1982) The influence of droperidol, diazepam, and physostigimine on ketamine-induced behavior and brain regional glucose utilization in rat. Anesthesiology 57:353–358

Olney JW, Farber NB (1995) Glutamate receptor dysfunction and schizophrenia. Arch Gen Psychiatry 52:998–1007

Olney JW, Labruyere J, Wang G, Wozniak DF, Price MT, Sesma MA (1991) NMDA antagonist neurotoxicity: mechanism and prevention. Science 254:1515–1518

Overall JE, Gorham DR (1962) The brief psychiatric rating scale. Psychol Rep 10:799–812

Øye I, Hustveit O, Moberg ER, Pausen O, Skoglund LA (1991) The chiral forms of ketamine as probes for NMDA receptor function in humans. In: Kameyama T, Nabeshima T, Domino EF (eds) NMDA receptor related agents: biochemistry, pharmacology, and behavior. NPP Books, Ann Arbor, Mich., pp 381–389

Øye N, Paulsen O, Maurset A (1992) Effects of ketamine on sensory perception: evidence for a role of *N*-methyl-D-aspartate receptors. J Pharmacol Exp Ther 260:1209–1213

Pandit SK, Kothary SP, Kumar SM (1980) Low dose intravenous infusion technique with ketamine: amnesic, analgesic and sedative effects in human volunteers. Anaesthesialogy 35: 669–675

Pardo JV, Pardo PJ, Janer KW, Raichle (1990) The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. Proc Natl Acad Sci USA 87:256–259

Restall J, Tully AM, Ward PJ, Kidd AG (1988) Total intravenous anesthesia for military surgery. A technique using ketamine, midazolam and vecuronium. Anesthesia 43:46–49

Restall J, Johnston IG, Robinson DN (1990) Flumazenil in ketamine and midazolam anesthesia. Anesthesia 45:938–940

Roache JD, Griffiths RR (1987) Lorazepam and meprobamate dose effects in humans:behavioral effects and abuse liability. J Pharmacol Exp Ther 243:978–988

Rothman SM, Olney JW (1987) Excitotoxicity and the NMDA receptor. Trend Neurosci 10:299–302

Rush CR, Higgins ST, Bickel WK, Hughes JR (1993) Acute effects of triazolam and lorazepam on human learning, performance and subject ratings. J Pharmacol Exp Ther 264:1218–1226

Salmaso D, Denes G (1982) Role of the frontal lobes on an attention task:a signal detection analysis. Percept Motor Skills 54:1147–1150

Sanders S (1986) The perceptual alteration scale: a scale measuring dissociation. Am J Clin Hypn 29:95–102

Siegel RK (1978) Phencyclidine and ketamine intoxication: a study of four populations of recreational users. In: Petersen RC, Stillman RC (eds) Phencyclidine (PCP) abuse: an appraisal, NIDA Research Monograph, Rockville, Md., 21, pp 119–147

Slosson RL (1963) Slosson intelligence test (SIT) for children and adults. Slosson Educational Publications, East Aurora, N.Y.

Smith DE, Wesson DR, Buxton ME, Seymour R, Kramer HM (1978) The diagnosis and treatment of the PCP abuse syndrome. In: Petersen RC, Stillman RL (eds) Phencyclidine (PCP) abuse: an appraisal. National Institute on Drug Abuse Monographs, US Government Printing Office, Washington D.C., 21, pp 229–240

Spitzer RL, Williams JBW, Gibbon M, First MB (1990) Structured clinical interview for DSM-III-R-non-patient edition (SCID-NP, Version 1.0). American Psychiatric Press, Washington, D.C.

Steinberg M, Rounsaville B, Cicchetti DV (1990) The structure clinical interview for DSM-III-R dissociative disorder: preliminary report on a new diagnostic instrument. Am J Psychiatry 147: 76–82

Stuss DT, Benson DF (1986) The frontal lobes. Raven Press, New York

Suzdak PD, Schwartz RD, Skolnick P, Paul SM (1986) Ethanol stimulates g-aminobutyric acid receptor-mediated chloride transport in rat brain synaptoneurosomes. Proc Natl Acad Sci USA 83:4071–4075

Thiemann S, Csernansky JG, Berger PA (1987) Rating scales in research: the case of negative symptoms. Psychiatry Res 20:47–55

Tobin HA (1982) Low-dose ketamine and diazepam. Arch Otolaryngol 108:439–440

Toft P, Romer U (1987) Comparision of midazolam and diazepam to supplement total intravenous anesthesia with ketamine for endoscopy. Can J Anaesth 34:466–469

Tucker MR, Hann JR, Phillips CL (1984) Subanesthetic doses of ketamine, diazepam, and nitrous oxide for adult outpatient sedation. J Oral Maxillofac Surg 42:668–672

Tuomisto J, Mannisto P (1985) Neurotransmitter regulation of anterior pituitary hormones. Pharmacol Rev 37:249–332

Weinberger DR, Berman KF, Zec RF (1986) Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. Arch Gen Psychiatry 43:114–124

White EL (1989) Cortical circuits, synaptic organization of the cerebral cortex structure, function, and theory. Birkhäuser, Boston, Mass.

White PF (1982) Comparative evaluation of intravenous agents for rapid sequence induction-thiopental, ketamine, and midazolam. Anesthesiology 57:279–284

White PF, Way WL, Trevor AJ (1982) Ketamine – its pharmacology and therapeutic uses. Anesthesiology 56:119–136

Wilkins AJ, Shallice T, McCarthy R (1987) Frontal lesions and sustained attention. Neuropsychologia 25:359–365

Willetts J, Balster RL, Leander JD (1990) The behavioral pharmacology of NMDA receptor antagonists. Trend Pharmacol Sci 11:423–428

Winer BJ (1971) Statistical Principles in Experimental Design, 2nd edn. McGraw-Hill, New York

Wise R, Chollet F, Hadar U, Friston K, Hoffner E, Frackowiak R (1991) Distribution of cortical neural networks involved in word comprehension and word retrieval. Brain 114:1803–1817

Wolkin A, Sanfilipo M, Wolf AP, Angrist B, Brodie JD, Rotrosen J (1992) Negative symptoms and hypofrontality in chronic schizophrenia. Arch Gen Psychiatry 49:959–965

Wolkowitz WM, Pickar D (1991) Benzodiazepines in the treatment of schizophrenia: a review and reappraisal. Am J Psychiatry 148:714–726

Wood JD, Hertz L (1980) Ketamine-induced changes in the GABA system of mouse brain. Neuropharmacology 19:805–808

Yamakura T, Mori H, Masaki H, Shimoji K, Mishina M (1993) Differential sensitivities of NMDA receptor channel subtypes to non-competitive antagonists. Neurorep 4:687–690

Zeilhofer HU, Swandulla D, Geisslinger G, Brune K (1992) Differential effects of ketamine enantiomers on NMDA receptor currents in cultured neurons. Eur J Pharmacol 213:155–158

Zsigmond EK, Domino EP (1980) Clinical pharmacology and current uses of ketamine. Trends in Intravenous Anesthesia Aldrite J, Stanley T (eds) Yearbook Medical Publishers, Chicago, IL, pp 283–328